NIH061.1CP1C2

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Lori et al.
Appl. No.	:	09/756,411
Filed	:	January 8, 2001
For	:	NEW PROCEDURE TO BLOCK THE REPLICATION OF REVERSE TRANSCRIPTASE DEPENDENT VIRUSES BY THE USE OF INHIBITORS OF DEOXYNUCLEOTIDES SYNTHESIS
Examiner	:	Crane, L.E.

Group Art Unit 1623

DECLARATION UNDER 37 CFR 1.132 OF DR. JORGE R. VILA

I, Dr. Jorge R. Vila, do hereby declare:

1. A true and correct copy of my Curriculum Vitae is attached as Exhibit 1.

2. The test methods using *quiescent* human peripheral blood lymphocyte (PBL) cells as outlined in Malley et al., Proc. Natl. Acad. Sci. USA 91:11017 (1994) (identifying synergistic effect of hydroxyurea and 2', 3'-dideoxyinosine (ddI)), of which I am the last-named author, are accepted by those skilled in the anti-human immunodeficiency virus (HIV) art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in vivo* and predictive from the *in vitro* tests using quiescent human PBL cells, as demonstrated by human clinical trials, per Vila et al., Lancet 350:635 (1997), of which I am the first-named author. Additionally, the test methods using *activated* human PBL

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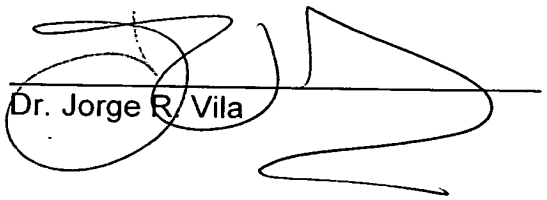
cells as outlined in Gao et al., Proc. Natl. Acad. Sci. USA 90:8925 (1993) and Lori et al., Science 266:801 (1994) (identifying synergistic effect of hydroxyurea and ddI) are also accepted by those skilled in the anti-HIV art as providing a reasonable basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo*, because the combination of hydroxyurea and ddI is effective *in vivo* and predictive from the *in vitro* tests using activated human PBL cells, as demonstrated by human clinical trials, per Vila et al., above. Although the test methods using quiescent human PBL cells may provide a *better* basis for a conclusion that the active agent under investigation will have utility for inhibiting replication of the virus in human cells *in vivo* (because viral DNA synthesis is known to take place in quiescent cells), the test methods using activated human PBL cells provide a *reasonable* basis for this conclusion (because a conclusion as to whether the combination would be effective *in vivo* was predictive from the *in vitro* tests), and a conclusion as to whether a specific anti-viral compound will in fact be effective *in vivo* is reasonably predictive from the *in vitro* tests using activated human PBL cells.

3. In view of the combination of hydroxyurea, a ribonucleotide reductase inhibitor, and ddI, a nucleoside reverse transcriptase inhibitor (NRTI), it is obvious that this principle should be viable for the combination of other NRTIs and that any modality that would deplete the intracellular pool of deoxyribonucleotide phosphates could substitute for hydroxyurea.

4. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Respectfully submitted,

Dated: February 27th, 2007

By: 
Dr. Jorge R. Vila

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CURRICULUM VITAE

VILA Jorge R.
Né le 3 Juin 1955 à Santa Fé Argentine.
Nationalité Argentine
Marié, trois enfant : Bérénice, M. (14/01/77)
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GRADES UNIVERSITAIRES :

Diplôme de Médecin-Chirurgien,
Université Nationale de Cordoba, Argentine
19/12/1978, moyenne : 9,31/10

POSTES HOSPITALIERS, UNIVERSITAIRES ET DE RECHERCHE :

Médecin Résident (service de chirurgie) l'Hôpital Aéronautique de Cordoba (Argentine), du 14/05/1979 au 31/03/1982.

Médecin Résident agrégé au Service de Cancérologie Clinique de l'Hôpital Aéronautique de Cordoba (Argentine), du 1/05/1979 au 31/03/1982.

Chef des Médecin Résident de l'Hôpital Aéronautique de Cordoba (Argentine), du 1/03/1982 au 29/12/1982.

Médecin Résident Etranger au Centre Léon Bérard (Lyon France) Service d'Oncologie Clinique du 1/02/1983 au 31/12/1984.

Attaché de Recherche au Centre Léon Bérard (Lyon France) :
Laboratoire d'Immunologie et de Cancérologie Expérimentale, INSERM U. 218 depuis le 1/01/1985

Responsable du groupe "Pharmacologie Moléculaire et Cellulaire des substances antitumorales", Laboratoire d'Immunologie et de Cancérologie Expérimentale du Centre Léon Bérard (Lyon France) depuis le 1/01/1989

BREVETS :

- 1. European Patent n° 87401398-0. Branch at the Hague, Netherlands, 21/07/1987. Médicament et composition médicamenteuse pour le traitement des tumeurs ainsi que pour le traitement des maladies infectieuses dues au virus. J.R. VILA, N. THOMASSET, A. EPSTEIN, F. WILD, & J-F. DORE.

- 2. European Patent n° 87401399-8. Branch at the Hague, Netherlands, 3/08/1987. Médicament pour le traitement des maladies infectieuses dues au virus, ainsi que pour le traitement des tumeurs. J.R. VILA, N. THOMASSET, A. EPSTEIN, & F. WILD

- 3. French patent 8905744, (déposé le 28/04/1989) : D-aspartique acide ß-hydroxamate en tant que médicament. J.R. VILA, N. THOMASSET, F. HAMEDI-SANGSARI, J. GRANGE. Demande d'extension internationale : PCT-FR 90/00307 (déposée le 27/04/1990)

LISTE DES PUBLICATIONS

1- PHILIP I., PHILIP T., FAVROT M., VILA J.R., FRAPPAZ D., BIRON P. & LENOIR G. Purging procedures are necessary to autologous bone-marrow transplantation in burkitt's lymphoma. In Cavalli ed., "Second International Conference on malignant Lymphoma", Lugano, Academic Publ., 1984.

2-PHILIP I., FAVROT M., VILA J.R., PINATEL C., BRANGER M. & PHILIP T., Detection of burkitt cells in remission marrow ; implication for autologus bone-marrow transplantation. 1st International Conference on Autologous bone-marrow transplantation. Houston, K. Dicke ed., 1985, pp 341-345.

3-VILA J.R., FAVROT M., PHILIP I., BRANGER M., BIRON P. & PHILIP T., In vitro cytolytic effects of ASTA-Z 7557 on clonogenic Burkitt cells potential value for a bone-marrow purging procedure. 1st International Conference on Autologous bone-marrow transplantation. Houston, K. Dicke ed., 1985, pp 461-465.

4- VILA J.R., THOMASSET N., NAVARRO C., & DORE J-F., *In vitro* and *in vivo* antitumor activity of L-glutamic acid γ-monohydroxamate against L1210 leukemia and B16 melanoma. *Int. J. Cancer*, **45**, 737-743 (1990).

5-DORE J-F., & VILA J.R., Melanoma cell secretion, CRC Press Inc. 1990, sous presse

6- GŒTSCH L, THOMASSET N, VILA J.R., PHILIP I., & DORE J-F., Selective effect of trichotecolone on hemopoietic tumor cells. *Anticancer Research*, **10**, 1013-1018 (1990)

7- THOMASSET N, HAMEDI-SANGSARI F, TOURNAIRE R, NAVARRO C, MALLEY S, GŒTSCH L, GRANGE J, & VILA J.R., Antitumoral activity of L and D isomers of aspartic ß-hydroxamate on L5178Y leukemia. *International Journal of Cancer*, under press.

8- TOURNAIRE R., ARNAUD S., HAMEDI-SANGSARI F., THOMASSET N., DORE J-F., VILA J.R., Therapeutic effects of a novel compound on Friend retrovirus disease in mouse. VII International Conference on AIDS, Florence (Italie), 16-21 june 1991.

9- GRANGE J., ESCAICH S., MALLEY S., TOURNAIRE R., THOMASSET N., HAMEDI-SANGSARI F., DUMONTET C., VILA J., Selective cytotoxic effect of D-aspartic β-hydroxamate (DAH) on hiv-1-infected cells in vitro. VII International Conference on AIDS, Florence (Italie), 16-21 june 1991.

10- BIRON F., DUMONTET C., VILA J.R., HAMEDI-SANGSARI F.,THOMASSET N., BOIBIEUX A., PERRET-LIAUDET A., PEYRAMOND D., Phase I/II study of the administration of D-aspartic β-hydroxamate (DAH) by continuous infusion to patients with AIDS. VII International Conference on AIDS, Florence (Italie), 16-21 june 1991.

11- THOMASSET N, GŒTSCH L, HAMEDI-SANGSARI F, NAVARRO C, VILA J.R., & DORE J.F., Antitumoral activity of L and D isomers of aspartic ß-hydroxamate on L5178Y leukemia. *International Journal of Cancer*, soumis.

12- VILA J.R., GRANGE J., HAMEDI-SANGSARI F., ESCAICH S., TOURNAIRE R., MALLEY S., GOETSCH L., DUMONTET C., & THOMASSET N., D-Aspartic acid ß-Hydroxamate is specifically cytotoxic for human cells infected by Human Immunodeficiency Virus type I. *Lancet*, soumis.

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Examiner	:	Crane, L.E.	

DECLARATION UNDER 37 CFR 1.132 OF NANCY W. VENSKO

I, Nancy W. Vensko, do hereby declare:

1. Dr. Jorge R. Vila, who made a Declaration under 37 CFR 1.132 in these proceedings, has a financial interest in the above-identified application.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/2/03

By: _____

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